CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 204447/000
Org. Code: 130
ity: 1
Stamp Date: 02-OCT-2012
PDUFA Date: 02-OCT-2013
Action Goal:
District Goal: 02-MAY-2013

Sponsor: TAKEDA PHARMS USA
1 TAKEDA PKY
DEERFIELD, IL 60015
Brand Name: Brintellix (vortioxetine)
Estab. Name:
Generic Name: Vortioxetine (LuAA21004)
Product Number; Dosage Form; Ingredient; Strengths
001; TABLET; VORTIOXETINE HYDROBROMIDE; 5MG
002; TABLET; VORTIOXETINE HYDROBROMIDE; 10MG
003; TABLET; VORTIOXETINE HYDROBROMIDE; 15MG
004; TABLET; VORTIOXETINE HYDROBROMIDE; 20MG

FDA Contacts:			
	W. WILSON-LEE	Prod Qual Reviewer	3017961651
	T. BOUIE	Product Quality PM	3017961649
	H. PATEL	Regulatory Project Mgr	3017962087
	C. TELE	Team Leader	3017961762

Overall Recommendation: ACCEPTABLE on 23-JUL-2013 by C. CAPACCI-DANIEL () 3017963532

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)
DMF No: **AADA:**
Responsibilities: FINISHED DOSAGE PACKAGER
Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE
Milestone: OC RECOMMENDATION
Milestone Date: 29-OCT-2012
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: **CFN:** 9613224 **FEI:** 3002807184
H. LUNDBECK A/S
ODDENVEJ 182, LUMSAS
NYK?BING, , DENMARK
DMF No: 21224 **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-JUL-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 9613225 **FEI:** 3002807185

H. LUNDBECK A/S
OTTILIAVE 9

VALBY, , DENMARK

DMF No: 21224 **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-JUL-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9613355 **FEI:** 3002807359

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-JUL-2013

Decision: ACCEPTABLE

P on: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-NOV-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9610992 **FEI:** 3002808311		
	TAKEDA PHARMACEUTICAL COMPANY LIMITED 17-85 JUSO-HONMACHI 2-CHOME		
	OSAKA, , JAPAN		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	07-DEC-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Brintellix (vortioxetine) Tablets

NDA 204-447

Summary Basis for Recommended Action
Chemistry, Manufacturing, and Controls

Applicant: Takeda Pharmaceuticals USA,
One Takeda Parkway
Deerfield, IL 60015

Indication: For the treatment of Major Depressive Disorder (MDD)

Presentation: The product will be available in four different strengths; 5 mg, 10 mg, 15 mg, and 20 mg. The different strength tablets are differentiated by color, and debossing markings. The tablets will be packaged in HDPE bottles for commercial distribution. Two physician sample presentations are also included.

EER Status: Overall recommendation is "Acceptable" as of 23-Jul-2013.

Consults: ONDQA Biopharmaceutics – Acceptable as per Dr. H. Mahayni's review dated 1-Jul-13.

Methods Validation – The methods were sent to FDA labs and were found to be acceptable for quality control and regulatory purposes (18-Jul-2013).

EA – Categorical exclusion granted.

Microbiology- Acceptable (J. Metcalfe, 1-May-13)

Post-Approval Agreements: None

Drug Substance:

The drug substance, vortioxetine hydrobromide, is a new molecular entity. The drug substance is a white to slightly beige crystalline solid that is highly soluble across physiological pH range. [redacted]

The CMC information for the drug substance manufactured by H. Lundbeck A/S is provided in the DMF [redacted]. This DMF was reviewed and found to be adequate to support the NDA. The drug substance quality is ensured through in-process controls throughout the manufacturing process and the appropriate final drug substance specification. The drug substance specification includes tests and acceptance criteria for drug substance critical quality attributes, e.g., description, identification, assay, impurities, particle size distribution, polymorph confirmation, residual solvents, [redacted], residue on ignition and residual [redacted]. The analytical procedures have been adequately described and validated to control the quality of the drug substance. The stability of the drug substance has been demonstrated through appropriate stability studies to support a retest period of [redacted].

Drug product:

Brintellix (vortioxetine) tablets is an immediate release film-coated tablet product to be marketed in four different strengths. The drug product formulation uses standard compendial excipients with all tablets having the same weight. [redacted] The film coat has different color pigments which impart distinct color to the tablets. The manufacturing process includes [redacted]. The applicant has used conventional in-process controls and end product testing to control the quality of the drug product. The end product specification includes testing for appearance, identification, assay, content uniformity, dissolution, and degradation products. The analytical procedures for the drug product testing are adequately described and validated. The provided stability data support a 36-month expiration period for this product.

The drug product is stored at 25°C [redacted]77°F). Excursions permitted 15-30ºC (59-86ºF).

Conclusion: Adequate from CMC perspective.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: The application is recommended for **"Approval"** from CMC perspective.

Ramesh K. Sood, Ph.D.
Division Director (Acting), DPA I/ONDQA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAMESH K SOOD
08/20/2013

NDA 204447
Review #2

Brintellix (vortioxetine) Tablets

Takeda Pharmaceuticals USA, Inc.

Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Quality Assessment
for
Division of Psychiatry Products

Table of Contents

Executive Summary Section

Chemistry Review Data Sheet

1. NDA: 204447

2. REVIEW: 01

3. REVIEW DATE: 26-JUL-2013

4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Review #1	29-MAY-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	28-JUN-2013
Amendment	19-JUN-2013
Amendment	31-MAY-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Takeda Pharmaceuticals USA, Inc.
Address:	One Takeda Parkway Deerfiled, IL 60015
Representative:	Joanna Sambor, MS Associate Director, Regulatory Affairs
Telephone:	224-554-2948

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Brintellix
b) Non-Proprietary Name (USAN): Vortioxetine
c) Code Name/# (ONDQA only): Lu AA21004; Lu AA21004-HBr
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 01 (NME)
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Tablet, Film-Coated

12. STRENGTH/POTENCY: 5 mg, 10 mg, 15 mg, 20 mg

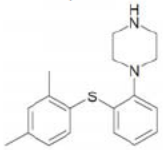
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed ___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 1-[2[(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine
Mol. Formula: $C_{18}H_{22}N_2S$
Mol. Weight: 298.45 (free base); 379.36 (HBr salt)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	1	Adequate	11-MAR-2013	
	III			3	Adequate	07-JUL-2010	Reviewed for NDA (b) (4)
	III			1	Adequate	08-MAR-2013	
	III			4	-	-	-
	III			3	Adequate	09-NOV-2012	Reviewed for NDA 203634
	III			4	-	-	-
	III			3	Adequate	28-JAN-2010	Reviewed for NDA 22511
				3	Adequate	06-MAR-2008	Reviewed for NDA 22262
				1	Adequate	08-MAR-2013	
	III			4	-	-	-
	III			3	Adequate	21-MAR-2012	Reviewed for NDA 203595
	III			1	Adequate	08-MAR-2013	
	II			1	**Adequate**	24-JUL-2013	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76307	Treatment of Depression
IND	112581	Treatment of Cognitive Dysfunction in Adult Patients with Major Depressive Disorder

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES	Acceptable.	23-JUL-2013	C. Capacci-Daniel
Pharm/Tox	Approval.	04-JUN-2013	A. Dow
ONDQA Biopharm	Approval.	01-JUL-2013	H. Mahayni
LNC	N/A	-	-
Methods Validation	Evaluated methods acceptable for quality control and regulatory purposes.	18-JUL-2013	M. Trehy
DMEPA	Proprietary name granted.	26-OCT-2012	L. Holmes
EA	Categorical Exclusion granted.	01-MAR-2013	W. Wilson-Lee
Microbiology	Approval.	01-MAY-2013	J. Metcalfe

Chemistry Review for NDA 204447

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend approval of Brintellix (vortioxetine) Tablets, from a Quality perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

We do not recommend any Phase 4 commitments, agreements, or risk management steps, from a Quality perspective.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Vortioxetine is a selective serotonin reuptake inhibitor. The drug product contains the β-polymorph of the drug substance as a hydrobromide salt (HBr). Vortioxetine HBr is a white to slightly beige powder that is highly soluble across the physiological pH range. H. Lundbeck A/S manufactures the bulk drug substance under DMF (b) (4). The proposed drug substance regulatory specification controls the appearance (visual); identification (FTIR, HPLC); assay (HPLC); (b) (4) impurities (HPLC, GC); (b) (4) residual solvents (GC); (b) (4); residue on ignition; particle size distribution (laser diffraction); and microbiological contamination. All drug substance analytical methods are appropriate and validated for their intended use. (b) (4) (b) (4)

Brintellix Tablets are immediate-release, film-coated tablets for oral administration, available in 5 mg, 10 mg, 15 mg, and 20 mg tablet strengths. The film-coat color and tablet debossing distinguishes the different tablet strengths. The formulation contains compendial excipients. The film-coat components are compendial. The drug product does not contain any novel excipients or excipients of human or animal origin.

Brintellix manufacturing (b) (4) (b) (4) The drug product is manufactured at two sites – H. Lundbeck A/S (Denmark) and Takeda Pharmaceuticals (Japan). The proposed regulatory drug product specification controls the appearance (visual); identification (UV and HPLC); degradation products (HPLC); content uniformity; dissolution (paddle method with HPLC); and assay (HPLC) of the drug product. The proposed drug product specification does not include a control for drug substance polymorphic form. All analytical methods are appropriate and validated for their intended use.

The applicant proposes three commercial packaging configurations and two physician sample configurations. The three commercial presentations for all tablet strengths include 30-count and 90-count 75 cc HDPE bottles and a 500-count 150 cc or 170 cc HDPE bottles. The two physician sample presentations include 7-count 45 cc HDPE bottles or 7-count blister cards. The proposed drug product container closures provide adequate protection from the environment, moisture, and light. The labeling

describes the drug substance and drug product and provides information about how the drug product is supplied and should be stored and handled.

Takeda proposes a 36 month drug product expiration dating period for all tablet strengths of Brintellix Tablets when stored in the commercial or sample packaging configurations. The proposed storage condition is 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature] (b) (4). Based on the stability data and in accordance with ICH Q1E, we assign a 36-month drug product expiration dating period when stored in the commercial and sample packaging under the recommended storage condition.

B. Description of How the Drug Product is Intended to be Used

The proposed indication for Brintellix Tablets is major depressive disorder. The proposed starting dose in adults is 10 mg, taken once daily without regard to meals. The proposed dose range is between 5 mg and 20 mg. Depending on individual response, patients may benefit from dose titration down to 5 mg or titration up to 20 mg.

C. Basis for Approvability or Not-Approval Recommendation

We recommend approval of the 5 mg, 10 mg, 15 mg, and 20 mg tablet strengths of Brintellix (vortioxetine) Tablets, from a Quality perspective. The drug substance DMF supporting the application was found adequate. The applicant revised the carton and container labels, patient labeling, and SPL data elements as recommended. The applicant also revised the proposed comparability protocols as recommended. The overall facilities recommendation is acceptable.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

Wendy I. Wilson-Lee, Ph.D.
Product Quality Reviewer
CDER/OPS/ONDQA/Division I/Branch I

B. Endorsement Block

WWilson-Lee: 26-JUL-2013
CTele: 26-JUL-2013
RSood: 29-JUL-2013

C. CC Block

HPatel:
TBouie:

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

WENDY I WILSON-LEE
07/29/2013

RAMESH K SOOD
07/29/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Wendy Wilson, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: wendy.wilson@fda.hhs.gov
Phone: (301)-796-1651
Fax: (301)-796-9747

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3815

Through: John Kauffman, Acting Deputy Director
Phone: (314) 539-2168

SUBJECT: Methods Validation Report Summary

Application Number: 204447

Name of Product: Vortioxetine Tablets, 5 mg, 10 mg, 15 mg, and 20 mg

Applicant: Takeda Global Research Development Center Inc.

Applicant's Contact Person: Joanna Sambor, Associate Director, Regulatory Affairs

Address: One Takeda Parkway, Deerfield, Illinois 60015

Telephone: (224) 554-2948 Fax: (224) 554-7870

Date Methods Validation Consult Request Form Received by DPA: 10/19/12

Date Methods Validation Package Received by DPA: 10/19/12

Date Samples Received by DPA: 12/11/12

Date Analytical Completed by DPA: 7/17/13

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments: See attached memo for summary of results and analyst's comments.

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63101
Tel. (314) 539-3897

Date: July 18, 2013

To: Wendy Wilson, CMC Reviewer

Through: John Kauffman, Deputy Director, Division of Pharmaceutical Analysis

From: Wei Ye, Chemist

Subject: Method Validation for NDA 204447
Vortioxetine Tablets
Takeda Globe Research Development Center Inc.

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. Determination of Impurity by GC
   (Takeda Global Research Development Center Inc., Analytical Procedure: 826-METH-401)

2. Determination of Impurity by HPLC
   (Takeda Global Research Development Center Inc., Analytical Procedure: 826-METH-331)

3. Assay and Degradation products
   (Takeda Global Research Development Center Inc., Analytical Procedure: Lu AA21004-18067)

4. Content Uniformity
   (Takeda Global Research Development Center Inc., Analytical Procedure: Lu AA21004-18068)

5. Dissolution
   (Takeda Global Research Development Center Inc., Analytical Procedure: Lu AA21004-18069)

Analyst's work sheets and data are available at http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8804a7690

- Determination of Impurity by GC
  (Takeda Global Research Development Center Inc., Analytical Procedure: 826-METH-401)

  Results:

  (b) (4)

- Determination of Impurity by HPLC
  (Takeda Global Research Development Center Inc., Analytical Procedure: 826-METH-331)

  (b) (4)

- Assay and Degradation products
  (Takeda Global Research Development Center Inc., Analytical Procedure: Lu AA21004-18067)

  Results:
  Assay

Dose	Sample	%LC	Avg. (2)
5 mg	Sample1	100.9	100.9
	Sample2	100.9	
20 mg	Sample1	98.9	98.6
	Sample2	98.2	

  Limit:
  90.0% - 110.0%

  Degradation
  No degradation products were found in 5 mg tablets or 20 mg tablets

  (b) (4)

- Content Uniformity
  (Takeda Global Research Development Center Inc., Analytical Procedure: Lu AA21004-18068)

  Results:

Dose	Tablet	%LC	Avg. (3)	SD	AV
5 mg	1	96.7	99.9	4.0	9.6
	2	104.4			
	3	98.6			
20 mg	1	95.8	97.1	5.1	13.6
	2	102.8			
	3	92.8			

Limit:
AV < 15.0

- Dissolution
  (Takeda Global Research Development Center Inc., Analytical Procedure: Lu AA21004-18069)

  Results:

Stage	Tablet	%Lu AA21004 Dissolved	
		5 mg	20 mg
S1	1	(b) (4)	
	2		
	3		
	4		
	5		
	6		
S2	1		
	2		
	3		
	4		
	5		
	6		
	Avg.(12):		

Limit:

Stage	Number Tested	Acceptance Criteria
S1	**6**	**Each unit is not less than Q + (b) (4). (Q= (b) (4))**
S2	**6**	**Average of 12 units (S1 + S2) is equal to or greater than Q, and no unit is less than Q - (b) (4).**

Reference: USP <711> Dissolution

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL L TREHY
07/18/2013

JOHN F KAUFFMAN
07/18/2013

NDA 204447

Brintellix (vortioxetine) Tablets

Takeda Pharmaceuticals USA, Inc.

Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Quality Assessment
for
Division of Psychiatry Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 204447

2. REVIEW: 01

3. REVIEW DATE: 15-MAY-2013

4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None.	-

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	03-MAY-2013
Amendment	25-APR-2013
Amendment	08-APR-2013
Amendment	07-MAR-2013
Amendment	13-FEB-2013
Amendment	20-DEC-2012
Amendment	12-DEC-2012
Original	02-OCT-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Takeda Pharmaceuticals USA, Inc.
Address:	One Takeda Parkway Deerfiled, IL 60015
Representative:	Joanna Sambor, MS Associate Director, Regulatory Affairs
Telephone:	224-554-2948

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Brintellix
b) Non-Proprietary Name (USAN): Vortioxetine
c) Code Name/# (ONDQA only): Lu AA21004; Lu AA21004-HBr
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 01 (NME)
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Major Depressive Disorder

11. DOSAGE FORM: Tablet, Film-Coated

12. STRENGTH/POTENCY: 5 mg, 10 mg, 15 mg, 20 mg

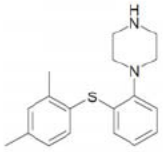
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed ___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 1-[2[(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine
Mol. Formula: $C_{18}H_{22}N_2S$
Mol. Weight: 298.45 (free base); 379.36 (HBr salt)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	1	Adequate	11-MAR-2013	
	III			3	Adequate	07-JUL-2010	Reviewed for NDA (b) (4)
	III			1	Adequate	08-MAR-2013	
	III			4	-	-	-
	III			3	Adequate	09-NOV-2012	Reviewed for NDA 203634
	III			4	-	-	-
	III			3 3 1	Adequate Adequate Adequate	28-JAN-2010 06-MAR-2008 08-MAR-2013	Reviewed for NDA 22511 Reviewed for NDA 22262
	III			4	-	-	-
	III			3	Adequate	21-MAR-2012	Reviewed for NDA 203595
	III			1	Adequate	08-MAR-2013	
	II			1	**Inadequate**	26-APR-2013	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	76307	Treatment of Depression
IND	112581	Treatment of Cognitive Dysfunction in Adult Patients with Major Depressive Disorder

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES	Pending.	-	
Pharm/Tox	Pending.	-	A. Dow
ONDQA Biopharm	Pending.	-	H. Mahayni
LNC	N/A	-	-
Methods Validation	Pending.	-	M. Trehy
DMEPA	Proprietary name granted. Pending.	26-OCT-2012	L. Holmes S. Hubert
EA	Categorical Exclusion granted.	01-MAR-2013	W. Wilson-Lee
Microbiology	Approval.	01-MAY-2013	J. Metcalfe

Chemistry Review for NDA 204447

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend a complete response action for Brintellix (vortioxetine) Tablets, from a Quality perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

We do not recommend any Phase 4 commitments, agreements, or risk management steps, from a Quality perspective.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Vortioxetine is a selective serotonin reuptake inhibitor. The drug product contains the β-polymorph of the drug substance as a hydrobromide salt (HBr). Vortioxetine HBr is a white to slightly beige powder that is highly soluble across the physiological pH range. H. Lundbeck A/S manufactures the bulk drug substance under DMF (b) (4). The proposed drug substance regulatory specification controls the appearance (visual); identification (FTIR, HPLC); assay (HPLC); (b) (4); impurities (HPLC, GC); (b) (4) content (ICP-OES); residual solvents (GC); heavy metals; residue on ignition; particle size distribution (laser diffraction); and microbiological contamination. All drug substance analytical methods are appropriate and validated for their intended use. (b) (4) (b) (4)

Brintellix Tablets are immediate-release, film-coated tablets for oral administration, available in 5 mg, 10 mg, 15 mg, and 20 mg tablet strengths. The film-coat color and tablet debossing distinguishes the different tablet strengths. The formulation contains compendial excipients. The film-coat components are compendial. The drug product does not contain any novel excipients or excipients of human or animal origin.

Brintellix manufacturing (b) (4) (b) (4). The drug product is manufactured at two sites – H. Lundbeck A/S (Denmark) and Takeda Pharmaceuticals (Japan). The proposed regulatory drug product specification controls the appearance (visual); identification (UV and HPLC); degradation products (HPLC); content uniformity; dissolution (paddle method with HPLC); and assay (HPLC) of the drug product. The proposed drug product specification does not include a control for drug substance polymorphic form. All analytical methods are appropriate and validated for their intended use.

The applicant proposes three commercial packaging configurations and two physician sample configurations. The three commercial presentations for all tablet strengths include 30-count and 90-count 75 cc HDPE bottles and a 500-count 150 cc or 170 cc HDPE bottles. The two physician sample presentations include 7-count 45 cc HDPE bottles or 7-count blister cards. The proposed drug product

container closures provide adequate protection from the environment, moisture, and light. The labeling describes the drug substance and drug product and provides information about how the drug product is supplied and should be stored and handled.

Takeda proposes a 36 month drug product expiration dating period for all tablet strengths of Brintellix Tablets when stored in the commercial or sample packaging configurations. The proposed storage condition is 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]; (b) (4)
Based on the stability data and in accordance with ICH Q1E, we assign a 36-month drug product expiration dating period when stored in the commercial and sample packaging under the recommended storage condition.

B. Description of How the Drug Product is Intended to be Used

The proposed indication for Brintellix Tablets is major depressive disorder. The proposed starting dose in adults is 10 mg, taken once daily without regard to meals. The proposed dose range is between 5 mg and 20 mg. Depending on individual response, patients may benefit from dose titration down to 5 mg or titration up to 20 mg.

C. Basis for Approvability or Not-Approval Recommendation

We recommend a complete response action of the 5 mg, 10 mg, 15 mg, and 20 mg tablet strengths of Brintellix (vortioxetine) Tablets, from a Quality perspective. The drug substance DMF supporting the application remains deficient. Revisions to the carton and container labels, patient labeling, and SPL data elements are recommended, from a CMC perspective. The proposed comparability protocols are inadequate. The overall facilities recommendation is pending.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

Wendy I. Wilson-Lee, Ph.D.
Product Quality Reviewer
CDER/OPS/ONDQA/Division I/Branch I

B. Endorsement Block

WWilson-Lee: 15-MAY-2013
CTele: 29-MAY-2013
RSood: 29-MAY-2013

C. CC Block

HPatel:
TBouie:

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/s/

WENDY I WILSON-LEE
05/29/2013

RAMESH K SOOD
05/29/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Wendy Wilson, CMC Reviewer
Chhagan Tele, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Wendy.Wilson@fda.hhs.gov
Phone: (301)-796 1651
Fax.: (301)-796 9747

Through: Ramesh Sood
Phone: (301)-796 1466
and
Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 204447

Name of Product: Vortioxetine Tablets, 5 mg, 10 mg, 15 mg, and 20 mg

Applicant: Takeda Global Research Development Center Inc.

Applicant's Contact Person: Joanna Sambor, Associate Director, Regulatory Affairs

Address: One Takeda Parkway, Deerfield, Illinois 60015

Telephone: (224) 554-2948 Fax: (224) 554-7870

Date NDA Received by CDER: **10/2/2012**

Date of Amendment(s) containing the MVP: **10/02/2012**

DATE of Request: **October 18, 2012**

Requested Completion Date: **1/18/2012**

PDUFA User Fee Goal Date: **7/25/2013**

Submission Classification/Chemical Class: NME

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package (MVP)

☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA # 204447

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
Vortioxetine Drug Substance and Drug Product Tablets, 5 mg, 10 mg, 15 mg, and 20 mg	Not specified	None

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	3.2.P.1
Specifications/Methods for New Drug Substance(s)	DMF (b) (4) 3.2.S.4.1/3.2.S.4.2
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5.1/3.2.P.5.2
Supporting Data for Accuracy, Specificity, etc.	See Item. 3
Applicant's Test Results on NDS and Dosage Forms	3.2.S.4.4 (DS) 3.2.P.5.4 (Dosage Form)
Other: MVP	3.2.R.

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
Drug Substance	Impurities by HPLC and GC	3.2.S.4.2.	**0**	DMF (b) (4): Impurities Method (826-METH-331 and 826-METH-401) Validation Report in 3.2.S.4.3
Drug Product	Identification, Assay and determination of degradation products by HPLC	3.2.P.5.2.	**0**	Degradation Products for 5, 10, 15, and 20 mg tablets. Method Validation Report in 3.2.P.5.3
Drug Product	Determination of content uniformity by HPLC	3.2.P.5.2.	**0**	Content Uniformity for 5, 10, 15, and 20 mg tablets. Method Validation Report in 3.2.P.5.3
Drug Product	Determination of Dissolution by HPLC	3.2.P.5.2.	**0**	Dissolution for 5, 10, 15, and 20 mg tablets. Method Validation Report in 3.2.P.5.3

Additional Comments:

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method

6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

CHHAGAN G TELE
10/19/2012

RAMESH K SOOD
10/19/2012

Office of New Drug Quality Assessment

Division of New Drug Quality Assessment I (Branch I)

Initial Quality Assessment

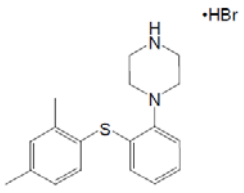
NDA 204447 (NME)

OND Division:	Division of Psychiatry Products
NDA:	204447
Applicant:	Takeda Global Research Development Center Inc.
NDA Filing Category:	505(b)(1)
Letter Date:	02-OCT-12
Stamp Date:	02-OCT-12
PDUFA Date:	25-JUL-13
Proposed Trade Name:	BRINTELLIX
Nonproprietary Name (USAN):	Vortioxetine/Vortioxetine HBr
Company Code Name:	Lu AA21004
Established Name:	NA
Dosage Form:	Immediate Release Tablet
Strengths:	5 mg, 10 mg, 15 mg, and 20 mg
Route of Administration:	Oral
Indication:	Treatment of Major Depressive Disorder (MDD)
Assessor:	Chhagan G. Tele, Ph.D.
ONDQA Fileability:	Yes

Background

The applicant submitted this NDA under section 505(b)(1) in an e-CTD format seeking approval for NME Vortioxetine (LuAA21004) tablets 5 mg, 10 mg, 15 mg, and 20 mg for the treatment of MDD. LuAA21004 belongs to a new chemical class of psychotropics, the bis-aryl-sulfanyl amines, which possess unique properties compared to currently known psychotropics. This new class of compounds is structurally different from all currently known psychotropics. Vortioxetine, which directly modulates serotonin receptors and inhibits serotonin reuptake, was discovered by H. Lundbeck A/S (Lundbeck) and has been co-developed by Lundbeck and Takeda Global Research & Development Center, Inc. (TGRD). The chemistry, manufacturing, and controls information of drug substance is the subject of the current IND 76,307 (TGRD, allowed 04-APR-2007) for the clinical evaluation for the treatment of MDD. The applicant indicated that Lu AA21004 has demonstrated efficacy in major depressive disorder at doses of 5 to 20 mg once daily in 6 of 9 short-term, placebo-controlled clinical studies in adults, 1 short-term placebo controlled study in the elderly, and 1 relapse-prevention study. The recommended starting dose in adults is 10 mg taken once daily without regard to meals. Several meetings (End of Phase 2, Pre-NDA CMC specific, Pre-NDA clinical, and Type C meeting) have been held with the sponsor prior to submission of the NDA to discuss the drug development program. Minutes of these meetings can be found in DARRTS and should be read by the reviewer. The reviewer needs to bridge any changes and agreements evolved from the meetings, amendments, and annual reports submitted during the drug development. The applicant provided Quality Overall Summary in the submission.

Structure of Vortioxetine HBr (LuAA21004-HBr)



Chemical Name: 1-{2-[(2,4-Dimethylphenyl)sulfanyl]phenyl}piperazine monohydrobromide

Drug Substance

Vortioxetine (LuAA21004) drug substance CMC information is cross-referenced to DMF (b) (4) [LoA dated 10-AUG-2012, H. Lundbeck A/S]. The drug substance will be manufactured commercially, tested (release and stability), and packaged by H. Lundbeck A/S, Lumsås, Denmark and Lundbeck Pharmaceuticals Italy S.P.A, Padova (PD), Italy sites. DMF (b) (4) will need to be reviewed and found adequate to support NDA. Additionally, the H. Lundbeck A/S, Ottiliavej 9, Denmark location will be used as an alternate site for control and release of Lu AA21004 hydrobromide. It is noted that drug substance is (b) (4) to meet particle size specification at the (b) (4) site. The reviewer needs to compare particle size data from both of these sites for the adequacy.

Vortioxetine HBr (LuAA21004-HBr) is white to very slightly beige powder. The chemical structure elucidation of Vortioxetine HBr (LuAA21004-HBr) drug substance has been confirmed by elemental analysis and different techniques of molecular spectroscopic analysis such as MS spectroscopy, ^{1}H and ^{13}C nuclear magnetic resonance (NMR), infrared (FTIR) absorption spectroscopy, and single crystal X-ray powder diffraction (XRPD). (b) (4) (b) (4) (b) (4) The physicochemical characteristics of the drug substance are defined by appearance, solubility, pH, dissociation constant, partition coefficient, hygroscopicity, and melting point.

In addition to information that is provided in the DMF, Takeda also provided analytical procedure for microbiological quality, which is not included in the DMF, but is used by Takeda. A summary of the validation data for Takeda's microbiological quality method Validation of Analytical Procedure and Certificates of Analysis for the drug substance batches is provided.

The proposed analytical test methods and corresponding limit should be reviewed with respect to the adequacy and justification of these methods and limits based on the available data obtained from batches at release and on stability studies (batch analysis), including organic, inorganic impurities and residual solvents and compliance to the ICH Q3 Guidances, in consultation with the Toxicology division. The impact of the physical properties of the drug substance, e.g., solubility, polymorph, particle size should be evaluated with respect to manufacturability, quality and performance of the drug product (immediate release solid oral dosage form). Harmonization of the acceptance specifications with the release specifications of the DMF holder should be considered.

Based on the stability data of the drug substance, the applicant has proposed retest date (b) (4) for the drug substance when stored in the proposed container closure system. Reviewer need to evaluate the quality and quantity of the stability data for the granting of the proposed retest period for the drug substance.

Drug Product

Vortioxetine drug product have been formulated into four strengths, 5 mg, 10 mg, 15 mg, and 20 mg IR tablets differentiated by tablet color and debossed marking. The marketed product will be available as follows: the 5 mg tablets are pink almond shaped biconvex film-coated tablet, with "5" debossed on one side and "TL" debossed on the other side; the 10 mg tablets are yellow, almond shaped biconvex film-coated tablet with "10" debossed on one side and "TL" debossed on the other side; 15 mg tablets are orange almond shaped biconvex film-coated tablet, with "15" debossed on one side and "TL" debossed on the other side, and 20 mg tablets are red almond shaped biconvex film-coated tablet with "20" debossed on one side and "TL" debossed on the other side.

Each tablet contains 6.355, 12.71, 19.065, or 25.42 mg of vortioxetine hydrobromide equivalent to 5, 10, 15, or 20 mg of vortioxetine, respectively. Inactive ingredients for the tablets include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate and film coating which consists of hypromellose, titanium dioxide, polyethylene glycol 400, iron oxide red (5, 15, and 20 mg) and iron oxide yellow (10 and 15 mg). All excipients are compendial grade. No novel excipients are used in the formulation. The applicant provided pharmaceutical and manufacturing process development studies to achieve required scale up, dissolution profile, and content uniformity. The assigned reviewer needs to review in detail about these studies for the compatibility and robust manufacturability of the drug product.

A selection of commonly employed excipients used in tablet manufacturing was evaluated in binary stability studies for compatibility with LuAA21004 hydrobromide. In addition, a series of prototype studies were carried out to determine the most robust combination of components and content. Four different IR tablet formulations of Lu AA21004 have been developed and evaluated with respect to stability and process ability: Formulation I, II, III, and IV. Formulation I demonstrated acceptable initial tablet stability but (b) (4) it was decided to develop a new tablet formulation, formulation II. During scale-up activities of formulation II, (b) (4) resulting in a formulation change to formulation III. The change from formulation III to formulation IV was required (b) (4) The change from formulation III to formulation IV also allowed for a (b) (4) improved manufacturing efficiency. Based on the results of both the binary stability studies, and the component studies, optimized formulation IV was selected for use in NDA registration and commercial tablets. An overall risk assessment of the drug product formulation components was performed to determine which formulation components have a high risk of impacting the drug product critical quality attributes (CQAs). The results of the initial formulation risk assessment are provided. The reviewer needs to review the adequacy of the risk assessment of formulation components.

The manufacturing process of the film-coated tablets was based on the physical and chemical properties of drug substances and historical knowledge. The manufacturing process has been provided (b) (4) For the manufacturing process of the commercial product, potential critical process parameters were identified and evaluated. The potential critical process parameters were identified and evaluated. All unit operations were assessed for their potential impact on quality attributes of the finished product using risk assessment/FMEA process. Of all the potential risks identified, the blend/content uniformity was identified as an area of potential risk needing further evaluation. From this initial evaluation, the following parameters were identified as requiring experimental investigation to define their statistical and practical significance:

(b) (4)

Summary of acceptable operating ranges for process parameters (b) (4) at commercial scale are provided. The reviewer needs to review the acceptability of operating ranges for process parameters (b) (4) to ensure the routine production of tablets having consistent high quality of the commercial scale manufacturing of the drug product.

Drug product tablets will be manufactured, released tested, and packaged for bulk shipment either of the following two sites, Takeda Pharmaceutical Company Limited, Osaka Plant, Japan and H. Lundbeck A/S Ottiliavej 9, Denmark. Primary packaging and labeling of the tablets into commercial containers will be performed (b) (4) .

Validated analytical methods are provided for the determination of ID (UV, HPLC), assay and degradation products (HPLC), content uniformity (HPLC), and dissolution (HPLC). The reviewer needs to look for the adequacy of the validation parameters.

The tablets are packaged in HDPE bottles and in (b) (4) film blister packaging. (b) (4)

Specification proposed for release of vortioxetine tablets are appearance, ID, assay, content uniformity, degradation product, and dissolution. The dissolution test method is performed in accordance with USP <711> using the USP Apparatus 2 (Paddle) at 50 rpm to determine the amount of drug substance released from the tablets. The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA Biopharmaceutics reviewer.

Batch analyses from three NDA registration batches manufactured at Takeda Pharmaceutical Company Limited. Analytical results for all batches of Lu AA21004 tablets used in clinical studies and primary stability studies are provided. Data from all tablet strengths and formulations used in clinical studies are included as supportive information for the investigational products. The formulations for each type are described in Section 3.2.P.2.2. The manufacturing sites referenced are: H. Lundbeck A/S (Valby, Denmark; hereinafter: Lundbeck) and Takeda Pharmaceutical Company, Osaka, Japan.

The primary stability studies are being performed on 3 lots each of Lu AA21004 tablets (5 mg, 10 mg, 15 mg and 20 mg) produced at pilot scale by H. Lundbeck A/S in Valby, Denmark. Stability of Lu AA21004 tablets in the proposed commercial packaging configurations, high density polyethylene (HDPE) bottle and (b) (4) blister, has been evaluated in a series of studies performed under conditions representing both long-term (25°C/60%RH) and short-term accelerated (40°C/75%RH) storage environments. Additionally, the samples were placed at an intermediate condition (30°C/65%RH) for use only in the event of significant change observed at the accelerated condition, per ICH Q1A (R2) guidance. The intermediate storage condition was not tested. For stability study in HDPE bottles at the long term (25°C/60%RH) storage condition, a matrix/bracket approach was utilized per ICH Q1D. The matrix/bracket study design for the primary stability lots was presented to the FDA in a Type C meeting request and briefing document (April 16 and May 27, 2010) and agreed by the FDA (preliminary response dated June 23, 2010 and Takeda final response dated June 29, 2010). Please refer to Section 2.0 for details of the matrix/bracket study design. The long-term testing is ongoing, and the studies are currently completed through the 18-month time point. The short-term accelerated testing is completed and finalized through 6 months. The stability data provided in this report includes the 6 month time point for accelerated condition and 18 month time point at long term condition.

Stability tests include: appearance, assay and degradation products, dissolution, water, hardness, and microbiology monitored in the stability program using validated methods. The sponsor also provided photostability results and indicated that vortioxetine tablets do not need protection from light exposure since the product is not photosensitive. The reviewer needs to confirm this statement by evaluating the provided data.

Based on stability data an expiration dating period of (b) (4) is proposed for vortioxetine tablets packaged in HDPE bottles in 7, 14, 30, 90, and 500-tablet count and unit-dose blister configuration when Store at 25° C (77° F); excursions permitted between 15° C and 30° C (59° F and 86° F).

Critical Review Issues

Drug Substance

- The NDA applicant references DMF (b) (4) [H. Lundbeck A/S] for CMC information on Vortioxetine (LuAA21004). DMF (b) (4) will need to be evaluated and found acceptable to support this NDA.
- (b) (4) The most stable solvent free form (β-form) is the form that is developed. (b) (4) The reviewer needs to evaluate the provided data to confirm that the selected β-form for the development is acceptable.
- (b) (4)
- Control strategy of potential impurities (including potential process impurities, potential genotoxic impurities) in the drug substance was discussed at both CMC specific and pre-NDA meetings held with the sponsor prior to submission of the NDA. The reviewer needs to bridge any changes and agreements evolved from these meetings, amendments, and annual reports submitted during the drug development.

Drug Product

- The compatibility of the excipients used in the drug product will need to be evaluated.
- Four different IR tablet formulations of Lu AA21004 have been developed and evaluated with respect to stability and process ability: Formulation I, II, III, and IV. Based on the results of both the binary stability studies, and the component studies, optimized formulation IV was selected for use in NDA registration and commercial tablets. An overall risk assessment of the drug product formulation components was performed to determine which formulation components have a high risk of impacting the drug product critical quality attributes (CQAs). The results of the initial formulation risk assessment are provided. The reviewer needs to review the adequacy of the risk assessment of the selected formulation components.
- For the manufacturing process of the commercial product, potential critical process parameters were identified and evaluated. The reviewer needs to review the adequacy of these potential critical parameters for the life cycle of the drug product.
- Summary of acceptable operating ranges for process parameters (b) (4)) at commercial scale are provided. The reviewer needs to review the acceptability of these operating ranges for process parameters to ensure the routine production of tablets having consistent high quality of the commercial scale manufacturing of the drug product.
- The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA Biopharmaceutics reviewer.
- Photostability results of the drug product are provided and indicated that the vortioxetine tablets do not need protection from light exposure since the product is not photosensitive. The reviewer needs to confirm this statement by evaluating the provided data.
- NDA submission contains no nanoscale materials. However, the reviewer should indicate that no nanoscale materials are present (see MAPP 5015.9 entitled, "Reporting Format for Nanotechnology—Related Information in CMC Review.")
- In the proposed labeling, the reviewer needs to confirm consistency in chemical structure, chemical name, molecular formula, and molecular weight of the drug substance with the current USP dictionary and USAN in the Description section of the labeling. Additionally, reviewer need to confirm that all the excipients used in the drug product formulation are included.

Comments and Recommendation:

The NDA is fileable from a CMC perspective. NDA submission does not have QbD elements (no design space, PAT, RTRT, reduced end-product testing etc.). However, it does contain an extensive pharmaceutical development section of the drug substance synthesis.

A claim for categorical exclusion under 21 CFR §25.31 (b) is provided in Module 1. In accordance with 21 CFR 25.15(d) and 21 CFR 25.31(b), Takeda Global Research Development Center, Inc. claims a categorical exclusion from the requirement for an Environmental Assessment or Environmental Impact Statement. In addition, the applicant states that to the best of their knowledge, no extraordinary circumstances exist that would preclude this claim for categorical exclusion. The approval of this application increases the use of the active moiety (Vortioxetine, LuAA21004), but the estimated concentration of the substance at the point of entry into the aquatic environment is below 1 ppb (0.028 ppb). The calculation of the Expected Introduction Concentration (EIC) of the active moiety into the aquatic environment is provided.

The list of manufacturing, testing, and packaging sites for drug substance and drug product is provided to enter into EES. The ONDQA PM will submit all manufacturing, testing, and packaging sites into EES. The reviewer will need to confirm that these sites are correct and that there are no additional sites that need to be entered. Assignment of the CMC portion of the NDA to a single reviewer is recommended. The ONDQA Biopharmaceutics team has to be consulted for review of the dissolution method and specification (Biopharmaceutics reviewer has not been assigned yet). It is recommended that the microbiology staff be consulted for evaluation of the microbiological controls.

A Methods Validation request will be submitted for the following analytical procedures:
Drug Substance:

- Determination of assay and impurities by HPLC.
- Determination of Residual Solvents by Headspace-GC

Drug Product:

- Determination of Identification, Assay and Degradation Products in Lu AA21004 film-coated tablets 5, 10, 15 and 20 mg by HPLC.
- Determination of Content Uniformity (CU) for LuAA21004 film-coated tablets 5, 10, 15 and 20 mg by HPLC method.
- Determination of Dissolution by HPLC.

This does not preclude the reviewer from identifying other analytical procedures for validation later in the review timeframe.

PRODUCT QUALITY: CMC AND BIOPHARMACEUTICS
FILING REVIEW FOR NDA

NDA Number: 204447	**Applicant:** Takeda Global Research Development Center Inc.	**Stamp Date:** 02-OCT-12
Drug Name: Vortioxetine (LuAA21004) IR Tablets	**NDA Type:** Standard	**Filing:**

CMC Reviewer: Wendy Wilson, Ph. D.
Biopharmaceuticals Reviewer: not assigned yet

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Applicant claims categorical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?			Biopharmaceutics reviewer needs to assess
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
34.	Does the application contain dissolution data?			Biopharmaceutics reviewer needs to assess related sections
35.	Is the dissolution test part of the DP specifications?			
36.	Does the application contain the dissolution method development report?			
37.	Is there a validation package for the analytical method and dissolution methodology?			
38.	Does the application include a biowaiver request?			
39.	Does the application include a IVIVC model?			
40.	Is information such as BCS classification mentioned, and supportive data provided?			
41.	Is there any in *vivo* BA or BE information in the submission?			

K. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
42.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		
43.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			NA
44.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
45.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

Chhagan Tele *04-OCT-12*

Name of Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Ramesh Sood

Name of Branch Chief Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHHAGAN G TELE
10/10/2012

RAMESH K SOOD
10/11/2012